REMARKS

Applicants respectfully request reconsideration of the present case in view of the above amendments and the following remarks. Applicants thank the Examiner for acknowledging the species election made on January 6, 2006. Applicants acknowledge the Examiner's election of a thiol species. Claims 1–26 are currently pending. Claim 1 has been amended. Claims 24–26 were withdrawn following a restriction requirement. No new matter has been inserted.

Rejection under § 112, first paragraph

The Examiner rejected claims 1–23 under § 112, first paragraph, for lack of enablement. Specifically, the Examiner states that the claims are not described in such a way as to enable a person of skill in the art to practice the methods of the invention. Applicants respectfully traverse this rejection.

To meet the enablement requirement, the disclosure in the specification must be sufficient to enable one of skill in the art to make and use the invention. In re Wands, 858 F.2d 731, 737 (Fed. Cir. 1988). A patent need not teach information well known in the art. Hybritech, Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1384 (Fed. Cir. 1986). The fact that experimentation may be complex does not make it undue, as long as the experimentation is routine or typical in the art. Wands, 858 F.2d at 737.

The present claims are directed to a method for separating glycosylated proteins from unglycosylated proteins in a mixture, with a resin including a nucleophile bound to a solid support via a linker. Glycosylated proteins are deglycosylated and covalently bound to a solid support as described in the specification. The technique is applicable to the separation of any sample containing a mixture of glycosylated and deglycosylated proteins, including O-glycosylated proteins, N-glycosylated proteins, C-mannosylated, phosphoglycosylated, etc.

Applicants submit that the specification enables the claimed subject matter without undue experimentation. As described in the specification, a mixture of glycoproteins and non-glycoproteins is contacted with a resin comprising a nucleophile. The mixture is contacted under conditions providing the β-elimination of the glycosyl group. See pages 11, line to page 12. An unsaturated group is at the sites of glycosylation which then forms a covalent bond with the resin. The β-elimination reactions are known to those of skill in the art and reaction conditions

that can provide for β-elimination at different glycosylation sites can be readily determined by those of skill in the art without undue experimentation. See page 19, lines 3-14 An example of the methods of the invention is provided at pages 521-523.

Any modifications required to the described methods, for a particular type of glycosylated protein, for example, would involve routine experimentation using information known in the art. In the methods described herein, a mixture containing glycosylated proteins is contacted with a resin comprising a nucleophile. It is known to those of skill in the art that the electron density of the amine nitrogen in the asparagine side chain is similar to the electron density of the hydroxyl oxygen in the serine-threonine side chain. A person of skill in the art would know to modify the conditions for contacting the resin to take into account minor differences in the chemistries of N-glycosylated and O-glycosylated peptides. Such modifications are routine in the art to which this invention belongs, and undue experimentation is not required.

The Examiner points to Wells et al. for the proposition that the invention is not enabled because Wells et al. indicates that "some of the O-GlcNAc-modified residues are more resistant to β-elimination." Applicants respectfully submit that the Wells et al. reference must be read as a whole. Wells et al. teaches that only mild β-elimination conditions were used so as to distinguish O-linked glycosylation sites from that of phosphorylated sites. Under such conditions, certain O-linked glycosylation sites were not readily subject to β-elimination. However, Applicants teach that phosphorylated sites can be removed through use of techniques known to those of skill in the art so that such mild β-elimination conditions taught by Wells et al. may not be required.

Applicants also respectfully disagree with the Examiner's contention that the Spiro article indicates the unpredictability of the glycopeptide art. Spiro is a review article, describing various glycopeptide linkages in well-characterized glycopeptides. The statement in Spiro referenced by the Examiner indicates only that a large number of glycopeptide linkages are known, providing a new avenue of research. However, in contrast to the Examiner's assertion, Spiro does not suggest that the chemistry of the glycosylation site linkages is unpredictable. The present claims are directed to methods of separating glycosylated and unglycosylated peptides. Any

experimentation required to separate glycosylated peptides with different linkages is routine in the art.

For the reasons indicated above, Applicants believe that the methods as claimed are enabled, and respectfully request withdrawal of the rejection.

Rejection under § 103

The Examiner rejected claims 1–9 and 11 under 35 U.S.C. § 103(a) as unpatentable over Wells et al. Applicants respectfully traverse this rejection.

The Examiner bears the initial burden of supporting any *prima facie* conclusion of obviousness. In order to establish a *prima facie* case of obviousness, three basic criteria must be met, namely: 1) the references must teach or suggest all of the claim limitations; 2) a suggestion or motivation to modify the reference must be present; and 3) the reference must provide a reasonable expectation of success. Applicants submit that all of these requirements have not been met.

The present claims are directed to methods for separating glycosylated proteins from unglycosylated proteins using a simplified process that eliminates multiple purification and clean-up steps needed to produce the final product. Claim 1, for example, recites contacting a mixture of glycosylated and unglycosylated proteins with a resin comprising a nucleophile bound to a solid support through a linker. The contact of sample and resin occurs under conditions that provide for β-elimination to deglycosylate the glycosylated peptides and form an unsaturated intermediate. The deglycosylated peptides are bound to the solid support through the unsaturated intermediate. Rinsing the solid support removes the unglycosylated proteins, and bound deglycosylated proteins are then released from the column. No additional purification or processing steps are required to provide the final product.

The Wells reference is directed to a method of mapping O-GlNAc sites after β-elimination. Solution-phase Michael addition is used to label glycosylation sites for proteins with either dithiothreitol (DTT) or biotin pentylamine and the products are analyzed using mass spectrometry (i.e. LC/MS). The methods described in Wells do not teach or suggest linking the unsaturated intermediate at the deglycosylation site to a resin comprising a nucleophile. The methods of Wells involve attaching a DTT or BAP using Michael addition and further purifying

using affinity purification. This reference thus does not teach or suggest direct coupling to a resin. In addition, Wells requires more clean-up and purification steps. For example, the samples are immunopurified using O-GlNAc specific antibodies (page 792), and peptides subjected to β-elimination are cleaned up using reverse-phase spin columns (page 793). The Examiner concedes that Wells does not teach a step where unglycosylated peptides are removed by rinsing.

There is no teaching or suggestion anywhere in the Wells reference that separation of the glycosylated peptides can or should be achieved using a method that results in deglycoslation protein bond to a solid support through an unsaturated intermediate. Without such a teaching, it cannot be said that it would have been obvious to modify the methods taught in Wells to arrive at the methods in the present claims. Furthermore, at least one of the claim limitations (i.e. removing unglycosylated proteins by rinsing) is not taught or suggested in Wells. Therefore, as all the limitations of the present claims are not disclosed in wells, the Examiner has not established a prima facie case of obviousness. Applicants respectfully request withdrawal of the rejection.

SUMMARY

In view of the above amendments and remarks, Applicant respectfully requests a Notice of Allowance. If the Examiner believes a telephone conference would advance the prosecution of this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,

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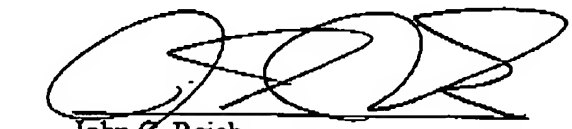

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